Remarks

Information Disclosure Statement

The Applicants note that an information disclosure statement for this application was filed with the patent office on March 8, 2004, and was received as indicated by the PTO-stamped return-receipt postcard. The Applicants thus respectfully request that the patent office sign off on the PTO Form 1449 and return it to the Applicants' representative.

Claim Rejections under 35 USC 112 first paragraph: Written Description

The patent office rejected claims 49, 54, 62, 65, and 67-75 under 35 USC 112 first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventors had possession of the invention at the time the application was filed. The applicants traverse this rejection.

"An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 1572 (Fed. Cir. 1997) and MPEP 2163.02. As specifically stated in this same MPEP section, "***Possession may be shown in a variety of ways***, including description of an actual reduction to practice, ***or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show the invention was complete***, or by ***describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention***." Thus, the MPEP clearly states that an actual reduction to practice is not required to satisfy the written description requirement.

Specifically, the patent office asserts that the confirmatory data provided in the Applicants' response to the previous office action did not include any data on SEQ ID NO:18, the elected species. This is clearly incorrect. As noted in the response, SEQ ID NO:18 has the amino acid sequence Arg-Val-Tyr-Ala-His-Pro-Phe [SEQ ID NO:18], as supported in the application as filed. The peptides tested and reported on in the response to the previous office action included **Ala4AIII; this is SEQ ID NO:18**, as is clearly

noted by the amino acid sequence accompanying the table showing the peptides tested (**RVYAHPF**), which uses the single letter amino acid code (for economy of space in the table presented in the declaration) rather than the 3 letter code, as used above. Thus, the apparent basis for the continued written description rejection of the currently pending claims is clearly incorrect.

Furthermore, the specification as filed provides support for the presently pending claims at, for example, page 8 lines 11-19; page 8 line 22 to page 9 line 3; and page 34 lines 6-12. Specifically, page 8 line 22 to page 9 line 3 states as follows:

> "The present invention fulfills the need for methods to enhance bone repair in a mammal suffering from bone fractures, defects, **and disorders which result in weakened bones such as osteoporosis, osteoarthritis, Paget's disease, osteohalisteresis, osteomalacia, periodontal disease, bone loss resulting from multiple myeloma and other forms of cancer, bone loss resulting from side effects of other medical treatment (such as steroids), and age-related loss of bone mass**."

Furthermore, on page 16 line 11 to page 17 line 6, the specification states:

> "**Another class of compounds of particular interest in accordance with the present invention** are those of the general formula II
>
> $$R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8$$
>
> in which R^2 is selected from the group consisting of H, Arg, Lys, Ala, Orn, Citron, Ser(Ac), Sar, D-Arg and D-Lys;
> R^3 is selected from the group consisting of Val, Ala, Leu, norLeu, Ile, Gly, Pro, Aib, Acpc and Tyr;
> R^4 is selected from the group consisting of Tyr, $Tyr(PO_3)_2$, Thr, Ser, homoSer, Ala, and azaTyr;
> R^5 is selected from the group consisting of Ile, Ala, Leu, norLeu, Val and Gly;
> R^6 is His, Arg or 6-NH_2-Phe;
> R^7 is Pro or Ala; and
> R^8 is selected from the group consisting of Phe, Phe(Br), Ile and Tyr.
>
> **A particularly preferred subclass of the compounds of general formula II has the formula**

R^2-R^3-Tyr-R^5-His-Pro-Phe [SEQ ID NO:16]
wherein R^2, R^3 and R^5 are as previously defined. Particularly preferred is angiotensin III of the formula Arg-Val-Tyr-Ile-His-Pro-Phe [SEQ ID NO:2]. **Other preferred compounds include peptides having the structures** Arg-Val-Tyr-Gly-His-Pro-Phe [SEQ ID NO:17] and **Arg-Val-Tyr-Ala-His-Pro-Phe [SEQ ID NO:18]**. The fragment AII(4-8) was ineffective in repeated tests; this is believed to be due to the exposed tyrosine on the N-terminus."

Therefore, it is clear that the Applicant provided a complete description of the claimed invention in the specification, and that the written description requirement was satisfied.

The patent office next argues that "it is still not described where SEQ ID NO:18 worked to increase bone growth in these weakened bones." This is also clearly inaccurate. As noted above, the declaration of Dr. Kathy Rodgers submitted together with the response to the previous office action clearly provides confirmatory data for the use of SEQ ID NO:18 according to the methods of the invention. As noted clearly in the declaration:

> 2. My laboratory has generated additional data, using the methods disclosed in the above-referenced patent application, Specifically, Sprague Dawley rats underwent intramuscular anesthesia with ketamine/rompum and were prepared for sterile surgery by shaving the surgical site and scrubbing with Betadine scrub followed by 70% ethanol. The rat was then placed on a sterile field in a lateral decubitis position facing the surgeon. The shaved legs were then covered with Betadine solution and draped aseptically. A skin incision was performed parallel to the long axis of the right medial diaphysis. The muscle was separated along fascial planes to expose the tibia. **A defect of 1.3 mm in diameter was then drilled from the lateral side of the midshaft cortex so that the defect extended from one cortical side to the other, through the bone marrow**. Sterile saline (0.9% NaCl) for injection was then used to clean the surgical area of tissue debris and bone fragments. Either hydron polymer solution (vehicle: 10% Hydron, 60% ethanol, 1% polyethylene glycol polymer) or **test peptide** in hydron polymer solution was placed in the bone defect to fill the defect with polymer (approximately 0.1 ml of polymer). The incision was closed with 3-0 Vicryl suture using continuous mattress suture. The animals were allowed to recover from anesthesia, given Bupronex for analgesia and allowed free movement, until euthanasia 7 days later.
>
> 4. By **gross observation, the defects that received peptides were more completely filled with new tissue that had begun to calcify**.

Microscopic evaluation of the tissue sections confirmed the gross observations. The vehicle-treated defects were filled with fibroproliferative tissue that was well vascularized. In the majority of vehicle treated defects, there was no callus formation and little osteoid formation. Occasionally, an osteoblast was observed at the site of injury.

6. Defects filled with peptide 2A (Lys^1-AIII) resulted in a large amount of fibroproliferative activity, callus formation and deposition of osteoid. In three of 5 tibia, the newly healing tissue appeared to displace the old bone. Similarly, defects filled with peptide 41A ($HomoSer^3$-AIII) had extensive callus formation, osteoid formation and fibroproliferative activity. Defects filled with peptide 2B (Lys^2-AII) resulted in a large amount of fibroproliferative activity, and callus formation. Defects filled with peptide 5A were filled with some fibroproliferative activity and osteoid formation. Bones treated with this peptide had extensive callus formation.

7. The remaining peptides (39B [$NorLeu^3$-AII], 22A **[Ala^4-AIII]**, A(1-9), 41B [$HomoSer^4$-AII], 39A ($NorLeu^2$-AIII) and AIII) had reduced activity compared with AII, peptide 2A, 2B, 5A and peptide 41A, **but the osteoid development was superior to vehicle control**.

Thus, the declaration clearly shows that Ala4AIII (SEQ ID NO:18) showed improved activity in treating the bone disorder than did vehicle. As such, SEQ ID NO:18 was shown to function according to the methods of the invention, in support of the application as filed. This is in addition to the various other peptides shown to be effective in the methods of the invention. Therefore, the patent office's assertion that the Applicants provided no description of the effect of SEQ ID NO:18 according to the methods of the invention is also incorrect.

The patent office further appears to be asserting that the percentage of study animals observed with new bone growth ("*only* 50%"), or the rate of new bone growth stimulated by the test peptides ("*low* rate") does not provide adequate evidence that the Applicants were in possession of the invention. First, the patent office provides absolutely no legal basis for the proposition that a positive treatment effect of a therapeutic on 50% of any patient class fails to provide adequate written description of the invention. Furthermore, the declaration provided by Dr. Rodgers states as follows:

5. In all of the **AII-treated animals**, there was extensive fibroproliferative and osteoblastic activity and new blood vessel growth. With AII treatment, callus can be seen external to the cortex as well as within the marrow space. The callus, within the marrow space, is composed of richly vascular fibroblastic tissue with peripheral areas of new bone formation. The new bone is characterized by innumerable, highly active osteoblasts surrounding islands of osteoid formation.

6. Defects filled with **peptide 2A (Lys^1-AIII)** resulted in a large amount of fibroproliferative activity, callus formation and deposition of osteoid. In three of 5 tibia, the newly healing tissue appeared to displace the old bone. Similarly, defects filled with **peptide 41A** (HomoSer^3-AIII) had extensive callus formation, osteoid formation and fibroproliferative activity. Defects filled with **peptide 2B (Lys^2-AII)** resulted in a large amount of fibroproliferative activity, and callus formation. Defects filled with **peptide 5A** were filled with some fibroproliferative activity and osteoid formation. Bones treated with this peptide had extensive callus formation.

7. The **remaining peptides** (39B [NorLeu^3-AII], 22A [Ala^4-AIII], A(1-9), 41B [HomoSer^4-AII], 39A (NorLeu^2-AIII) and AIII) had **reduced activity compared with AII, peptide 2A, 2B, 5A and peptide 41A, <u>but the osteoid development was superior to vehicle control</u>**.

Thus, the declaration makes clear that **<u>all of the peptides tested provided a benefit in treating the tested bone disorder and stimulating increased bone growth.</u>** Furthermore, each of the tested peptides was more effective than control, with some of the peptides having increased activity relative to other peptides.

Based on all of the above, it is clear that the applicants were in possession of the claimed invention, as per MPEP 2163.02, and thus the written description requirement of 35 USC 112 first paragraph has been met. Therefore, the Applicants respectfully request reconsideration and withdrawal of the written description rejection.

Claim Rejections under 35 USC 112 first paragraph: Enablement/Scope

The patent office rejected claims 49, 54, 62, 65, and 67-75 under 35 USC 112 first paragraph as containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to make and/or use the invention. Specifically, the patent office asserts that the specification does not enable the use of

SEQ ID 18 according to the claimed methods, nor for using any peptides for preventing bone disorders that result in weakened boned. The applicants traverse this rejection.

In order to satisfy the enablement requirement, an Applicant must teach those of skill in the art to make and use the claimed invention without undue experimentation. MPEP 2164. Factors considered in analyzing undue experimentation include claim breadth, the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of unpredictability in the art; the amount of direction provided in the specification; the existence of working examples; and the quantity of experimentation necessary to make or use the invention (MPEP2164.01(a)). "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject mater sought to be patented **must be taken as being in compliance with the enablement requirement...unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."** (MPEP 2164.04).

As an initial matter, it is noted that the patent office has admitted that the specification enables the scope of the claim with respect to SEQ ID Nos: 1, 4, and 45 (see page 7, first paragraph of previous office action, as well as page 4 of the current action). The patent office further indicated that the specification is enabling for methods of treating bone disorders that result in weakened bones. (See page 7, second full paragraph of previous office action, as well as page 4 of the current action.) It is further noted that no further legal analysis is provided by the patent office to assess whether one of skill in the art can make or use the claimed invention without undue experimentation. Instead, the patent office has simply asserted (a) that no confirmatory data was shown for SEQ ID NO:18; and (b) that, given the lack of confirmatory data for SEQ ID NO:18, those of skill in the art would not accept that the confirmatory data correlates with the use of SEQ ID NO:18 to effectively treat a bone disorder that results in weakened bone growth.

The patent office asserts that the confirmatory data provided in the Applicants' response to the previous office action did not include any data on SEQ ID NO:18, the elected species. This is clearly incorrect. As noted in that response (and as discussed above), SEQ ID NO:18 has the amino acid sequence Arg-Val-Tyr-Ala-His-Pro-Phe [SEQ

ID NO:18], as supported in the application as filed. The peptides tested and reported on in the response to the previous office action included **Ala4AIII; this is SEQ ID NO:18**, as is clearly noted by the amino acid sequence accompanying the table showing the peptides tested (**RVYAHPF**), which uses the single letter amino acid code (for economy of space in the table presented in the declaration) rather than the 3 letter code, as used above. Thus, the apparent basis for the continued written description rejection of the currently pending claims is clearly incorrect. The patent office next argues that "it is still not described where SEQ ID NO:18 worked to increase bone growth in these weakened bones." This is also clearly inaccurate. As noted above, the declaration of Dr. Kathy Rodgers submitted together with the response to the previous office action clearly provides confirmatory data for the use of SEQ ID NO:18 according to the methods of the invention. As noted clearly in the declaration:

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> 4. By **gross observation, the defects that received peptides were more completely filled with new tissue that had begun to calcify. Microscopic evaluation of the tissue sections confirmed the gross observations**. The vehicle-treated defects were filled with fibroproliferative tissue that was well vascularized. In the majority of

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composed of richly vascular fibroblastic tissue with peripheral areas of new bone formation. The new bone is characterized by innumerable, highly active osteoblasts surrounding islands of osteoid formation.

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Thus, the declaration makes clear that **all of the peptides tested provided a benefit in treating the tested bone disorder and stimulating increased bone growth.** Furthermore, each of the tested peptides was more effective than control, with some of the peptides having increased activity relative to other peptides.

Finally, the Applicants note that those of skill in the art can make and use the claimed invention without undue experimentation. Using the methods as disclosed in the invention, Dr. Rodgers demonstrated the effective use of a number of other peptides as claimed. The level of skill in the art is very high, the claims were previously amended to narrow their scope, and the specification as filed contains a number of working examples and much guidance. This provides further demonstration that the claims are enabled by the specification.

Based on all of the above, it is clear that the present invention contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject mater sought to be patented. Thus, the application **must be taken as being in compliance with the enablement requirement...unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."** (MPEP 2164.04).

The patent office has provided absolutely no reason to doubt the objective truth of the statements contained in the application or in the declaration, and has in fact relied on incorrect assumptions in affirming the rejection based on non-enablement.

Thus, the Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim Rejections under 35 USC 112 second paragraph

Claims 49, 54, 62, 65, and 67-75 were rejected under 35 USC 112 second paragraph as indefinite, based on the assertion that the recitation of the genus rendered the claim indefinite to one of skill in the art, as it is drawn to encompass use of sequences outside of the elected sequence. The applicants traverse this rejection.

As stated in 37 CFR 1.146 (and amplified on in MPEP 809.02):

> "In the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable. However, if such application contains claims directed to more than a reasonable number of species, the examiner may require restriction of the claims to not more than a reasonable number of species before taking further action in the application"

In the present case, the application was filed with independent claim 49, which was generic to the species recited by the patent office in the restriction requirement of August 21, 2003. Thus, the patent office, in making a restriction requirement, should have required the election of a species to which the claims would be restricted if no generic claim were found to be allowable (See, for example, the form paragraph 8.01 on "Election of Species" in MPEP 809.02(a)), or required restriction of the claims to not more than a reasonable number of species (Form paragraph 8.02). Instead, the patent office required election of an invention as defined by species recited in dependent claims 54-56 and 62-64.

The Applicants have subsequently amended generic claim 49 to recite a fairly narrow genus that encompasses elected species SEQ ID NO:18. The Applicants thus respectfully request that the patent office consider the generic claims, and limit the claims

to the elected species if the genus claims are found to not be allowable, as per 37 CFR 1.146. The Applicants note the tremendous burden placed upon them and the patent office to separately prosecute patents claiming methods using a single peptide, when generic claims of reasonable scope that are fully enabled are available.

Claim rejections under 35 USC 112 second paragraph: Indefiniteness

The patent office rejected claims 49, 54, 62, 65, and 67-75 as being indefinite because the claims are drawn to sequences outside of the elected sequence. The Applicants traverse this rejection.

All of the pending claims are readable on the elected species, SEQ ID NO:18. As stated in 37 CFR 1.141, "[M]ore than one species of an invention, not to exceed a reasonable number, may be specifically claimed in different claims in one national application, provided the application also includes an allowable claim generic to all of the claimed species and all the claims to species in excess of one are written in dependent form...or otherwise include all of the limitations of the generic claim." See also MPEP 806.04(a).

Furthermore, 37 CFR 1.146 states "In the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable. However, if such application contains claims directed to more than a reasonable number of species, the examiner may require restriction of the claims to not more than a reasonable number of species before taking further action in the application."

In the present case, the patent office is asserting that the claims are indefinite because they contain generic claims not limited to the elected species, SEQ ID NO:18. Those of skill in the art would not find these claims indefinite, as the metes and bounds of the claims are clearly delineated, and since the inclusion of such generic claims are clearly contemplated by the rules governing patent applications embodies in the CFR, as well as in MPEP 806.04(a).

Pending claim 49 recites a genus that encompasses elected species SEQ ID NO:18. All of the other claims are dependent on claim 49, and no species other than SEQ ID NO:18 is recited in the claims. While the Applicants note that they are entitled to a reasonable number of species, as per the rules cited above, the patent office has required election of only a single species. In order to expedite prosecution, the Applicants have limited the claims to recitation of only a single species. However, the patent office's "strong suggestion" that the complete scope of the claims be limited specifically to elected species SEQ ID NO:18 is contrary to patent office restriction practice, as discussed above, and also imposes a huge burden on the Applicants, who would thus be required to file an enormous number of divisional applications simply to pursue claims of scope to which they are entitled. This is unduly burdensome on the Applicants, and provides no benefit to the patent office, as such a practice would greatly increase the number of pending applications.

Thus, the Applicants respectfully request reconsideration and withdrawal of the rejection.

In light of the above amendments and arguments, the applicants believe that the application is now in condition for allowance. If there are any questions about this response, the Examiner is respectfully requested to call the below-signed attorney for the Applicants at (312) 913-2106.

Respectfully submitted,

McDonnell Boehnen Hulbert & Berghoff

Date: 8/2/04

By: _____

David S. Harper
Reg. No. 42,636